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Yaeta Endo

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400 HOLIDAY COURT

SUITE 102

WARRENTON, VA 20186

EXAMINER

BRISTOL, LYNN ANNE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/522,000	Applicant(s) ENDO ET AL.	
	Examiner LYNN BRISTOL	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-7,9 and 20-29 is/are pending in the application.
- 4a) Of the above claim(s) 25-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-7, 9, 20-24, 28 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/08 has been entered.
2. Claims 1, 2, 5, 6, 7, 9, and 20-29 are all the pending claims for this application.
3. Claims 3, 4, 12-16, 18, and 19 are cancelled, Claims 1, 2, 5-7, 9, 20, 21, 23, and 24 were amended and new Claim 29 was added.
4. Claims 25-27 are withdrawn from examination.
5. Claims 1, 2, 5-7, 9, 20-24, 28 and 29 are all the pending claims under examination.
6. Applicants amendments to the claims have necessitated new grounds for objection and rejection.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

7. The rejection of Claims 2-9 for the recitation that the antibody “carries” or is “carrying” a labeling substance in the linker part is withdrawn in view of the amendments to cancel the claims or amend the claims to delete the phrase.

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8. The rejection of Claim 9 for the recitation the antibody “has a Kd value that is equivalent to a Kd value of a naturally occurring antibody” is withdrawn in view of the amendment to the claim to recite “parental antibody.”

9. The rejection of Claims 3, 4, 7, 8 and 21-24 and 28 for the recitation “labeling substance is a substance that is capable of binding to a polypeptide of the linker part of the antibody in the presence of a specific enzyme” in Claims 3, 4, 7, 8 and 21 (elements 3, 4, 7 and 8) because it is not clear what the relationship is between the labeling substance that is bound to the linker and the polypeptide that is part of the linker is withdrawn.

The claims have been cancelled or amended to more clearly set forth the structural relationship between the linker, the labeling substance and the enzyme.

10. The rejection of Claim 20 for the recitation “wherein DNA is subjected to transcription and translation utilizing a wheat embryo-derived cell-free protein translation system in the presence of a labeling substance and an enzyme that catalyzes a disulfide bond exchange reaction” is withdrawn in view of the amendment to more clearly set forth the structural relationship between the linker, the labeling substance and the enzyme.

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11. The rejection of Claim 20 for the recitation “the DNA encoding the linker comprises a nucleotide sequence that is capable of binding with a labeling substance in the presence of a specific enzyme after translation” is withdrawn in view of the deletion of the phrase from the claim.

Claim Rejections - 35 USC § 103

12. The rejection of Claims 1, 9, 21 and 28 under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al. (Peptides 24:353-362 (March 2003) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07) is withdrawn in view of the amendment of the claims.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. The rejection of Claims 5 and 6 under 35 U.S.C. 102(a) as being anticipated by Pavlinkova et al. (Peptides 24:353-362 (March 2003)) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 11/26/07 as follows:

“The interpretation of Claims 1, 2, 5, 6, 21, 23 and 24 is of record as set forth in the Office Action of 6/11/07. Claims 1 and 21 have been amended and are now interpreted as being drawn to the single chain antibody having a heavy and light chain being directly crosslinked through a linker where the linker is bound to a labeling substance

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(Claim 1), and a method for producing the immobilized single chain antibody on a surface which is reacted with a substance that specifically binds the labeling substance where the heavy and light chain are crosslinked through a linker and the linker binds to the labeling substance (element 1) of Claim 21) or the heavy and light chain are variable regions (element 2) of Claim 21) or the labeling substance is incorporated as one part of the linker (element 5) of Claim 21) or the heavy and light chain are variable regions and the labeling substance is incorporated as one part of the linker (element 6) of Claim 21).

Pavlinkova disclose scFv antibodies containing strepavidin-binding peptide or a biotin-like mimic peptide (BMP) where the scFv is modified to contain the BMP. The dimeric scFv comprises VL-linker-VH-linker-VL-linker-VH where the BMP having amino acid sequence SAWRHPQFGG was added to the carboxyl terminus of the VH region by adding the nucleotide sequence shown in figure 1 (Materials and Methods, p. 354, Col. 2, ¶2). One of ordinary skill in the art would reasonably interpret that the addition of the BMP to the C-terminus of the VH domain could occur at either VH domain for the dimeric scFV such as: VL-linker-VH-BMP-linker-VL-linker-VH or VL-linker-VH-BMP-linker-VL-linker-VH-BMP or VL-linker-VH-linker-VL-linker-VH-BMP absent a showing to the contrary. The first and second embodiments of the dimeric scFv would require that the labeling substance, BMP, bind to the linker vis-à-vis a fusion as taught by Pavlinkova. Pavlinkova teaches expressing the scFvs in Yeast expression systems, detecting the scFvs by ELISA where the single chain antibody would be immobilized, reacting the scFvs with streptavidin to form a complex. Pavlinkova teaches that another scFv-BMP molecule recognizing CA125, had also been generated by others, thus the insertion of a biotin-like or BMP labeling substance within the linker or binding to the linker vis-à-vis a fusion was already known in the art (p. 359, Col. 1, ¶2) and one could readily envisage the combination of scFv-BMP molecules. Pavlinkova teaches that the immunoreactivity of the single chain antibody was unchanged compared to the parent scFV (p. 359, Col.2, ¶2). Pavlinkova teaches that a labeling substance can block the binding sites or hinder the binding of the conjugate to the targeting moiety, but that insertion of the BMP into a strictly defined site ensures that the immunoreactivity is retained.

It is noted that the labeling substance of the instant invention is not limited to the peptide of SEQ ID NO: 11 as shown in Figure 1 of the instant specification, therefore any biotin peptide or BMP as taught by Pavlinkova anticipates the claimed single chain antibody."

Applicants' allegations on pp. 13-14 of the Response of 5/22/08 have been considered but are not found persuasive. Applicants' allege that in amending Claims 1, 20 and 21 to recite that "the linker comprises an amino acid sequence that is recognizable by a biotin ligase, and wherein the biotin ligase binds the labeling substance to the linker", that the claims are distinguishable from Pavlinkova.

Response to Arguments

Claim 5 is now interpreted as encompassing a single chain antibody comprising a heavy chain and a light chain cross-linked through a linker and where the linker comprises a labeling substance incorporated as one part of the linker. Applicants have not addressed instant pending claims 5 and 6 in the Response. As stated on the record, Pavlinkova teaches a single chain antibody comprising a biotin mimetic peptide (BMP) fused to the carboxy terminus of the VH domain. Pavlinkova does not state which of the

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two VH domains are fused to BMP, thus the embodiments suggested by Pavlinkova's disclosure are structures for VL-linker-VH-BMP-linker-VL-linker-VH or VL-linker-VH-BMP-linker-VL-linker-VH-BMP, where the BMP labeling substance is technically and structurally incorporated as one part of the linker. The claims do not recite where within the linker the labeling substance should be incorporated. Thus a region of an antibody implicit to Pavlinkova is the domain "BMP-linker", which is interpreted as the substance incorporated in the linker part.

The rejection is maintained.

New Grounds for Objection

Claim Objections

14. Claim 21 is objected to because of the following informalities: the claim fails to indicate whether the antibodies for each of elements 1)-4) are in the alternative or inclusive. In other words, Applicants should consider amending the claim to insert the term "or" or "and" between elements 3) and 4). Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1, 2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibling et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07).

Claims 1, 2 and 7 are interpreted as being drawn to a labeled single chain antibody comprising a heavy and light chain of an antibody directly crosslinked through a linker with the linker comprising an amino acid sequence recognized by biotin ligase where the ligase binds a labeling substance to the linker and the linker is bound to the labeling substance (Claim 1), the heavy and light chains of Claim 1 are variable regions (Claim 2), and the labeling substance of Claim 1 is biotin (Claim 7).

The claimed single chain antibodies were prima facie obvious at the time of the invention over Silber as evidenced Weiss and Pavlinkova.

Sibling teaches bacterially expressed Fab/BCCP proteins comprising VH-CH1, Vk-Ck and a BCCP domain (biotin carboxy carrier protein) encoded by a DNA vector (Figure 1, first vector scheme) as evidenced by Weiss, and where further downstream in the DNA vector a gene for a BirA protein (biotin holoenzyme synthetase) is cloned into

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the first construct of Weiss (Figure 1, third vector scheme). Sibling teaches the intracellular BirA activity in bacteria transformed with the DNA encoding pFab4/BCCP increased the amount of biotinylation of the disulfide linked protein. Sibling discloses a Fd (VH-CH1)-BCCP fragment being disulfide bonded to the Vk-Ck chain and having increased biotin labeling of the BCCP domain because of the increased expression of BirA. It is noted that the labeling region of the linker of the instant invention is not limited to the peptide of SEQ ID NO: 11 as shown in Figure 1 of the instant specification. Silber does not disclose single chain antibodies (e.g., scFvs) being directly crosslinked with a linker where the BCCP domain is integrated into the structure but indicates that single chain Fvs (scFvs) which are smaller and generally expressed at higher levels in bacteria than Fab may be efficiently biotinylated in vivo. Pavlinkova discloses scFvs comprising a linker and a labeling substance.

Pavlinkova discloses scFv antibodies containing streptavidin-binding peptide or a biotin-like mimic peptide (BMP) where the scFv is modified to contain the BMP. The dimeric scFv comprises VL-linker-VH-linker-VL-linker-VH where the BMP having amino acid sequence SAWRHPQFGG was added to the carboxyl terminus of the VH region by adding the nucleotide sequence shown in figure 1 (Materials and Methods, p. 354, Col. 2, ¶2). One of ordinary skill in the art would reasonably interpret that the addition of the BMP to the C-terminus of the VH domain could occur at either VH domain for the dimeric scFV such as: VL-linker-VH-BMP-linker-VL-linker-VH or VL-linker-VH-BMP-linker-VL-linker-VH-BMP or VL-linker-VH-linker-VL-linker-VH-BMP absent a showing to the contrary. The first and second embodiments of the dimeric scFv would require that

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the labeling substance, BMP, bind to the linker vis-à-vis a fusion as taught by Pavlinkova. Pavlinkova teaches expressing the scFvs in Yeast expression systems, detecting the scFvs by ELISA where the single chain antibody would be immobilized, reacting the scFvs with streptavidin to form a complex. Pavlinkova teaches that another scFv-BMP molecule recognizing CA125, had also been generated by others, thus the insertion of a biotin-like or BMP labeling substance within the linker or binding to the linker vis-à-vis a fusion was already known in the art (p. 359, Col. 1, ¶2) and one could readily envisage the combination of scFv-BMP molecules. Pavlinkova teaches that the immunoreactivity of the single chain antibody was unchanged compared to the parent scFV (p. 359, Col.2, ¶2).

One skilled in the art would have been motivated to have produced and been reasonably assured of success having produced the instant claimed antibody over Silber as evidenced by Weiss and Pavlinkova. Each of the references teaches antibody fragments comprising the VH and VL domains of a corresponding antibody which are disulfide linked and which comprise a region for biotinylation (Silber) or a biotinylation mimetic domain (Pavlinkova). Silber provides sufficient motivation to consider generating or modifying small antibody fragments for ease of selection where the antibody is directly bound to biotin during the intracellular expression process taking advantage of endogenous biotin ligase within the E. coli and by increasing the degree of biotinylation with a co-engineered biotin ligase. Because both references teach the techniques for generating scfvs, the ordinary artisan could have modified the scfv of Pavlinkova by introducing the BCCP domain of Silber into the construct especially in a

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region such as the linker being away from the variable domains to avoid steric hindrance with binding to antigen. Pavlinkova teaches that a labeling substance can block the binding sites or hinder the binding of the conjugate to the targeting moiety, but that insertion of the BMP into a strictly defined site ensures that the immunoreactivity is retained. Pavlinkova teaches and appreciates that the engineered construct assures consistency of quality and structure (p. 359, Col. 2, ¶2). Thus to generate a scfv comprising a linker containing the BCCP domain being recognized by biotin ligase, was obvious in view of Silber and Pavlinkova in order to retain antigen binding but to facilitate biotin labeling for antibody screening and selection. Expressed scFvs that are naturally biotinylated would eliminate in vitro chemical biotinylation procedures in order to avoid conditions that are deleterious for binding activity and the binding capacity is virtually identical to the parent antibody (Silber, p. 138, Col. 2, ¶1). Thus to generate the instant claimed antibody would have been reasonably expected because a similar construct had already been generated by Pavlinkova where in view of Silber, the amount of biotinylation could be enhanced with the BCCP domain in the presence of increased biotin ligase expression. The claimed invention was prima facie obvious.

16. Claims 1, 9 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) as applied to claim 1

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above, and further in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07).

The interpretation of Claim 1 is discussed above under section 14. Claim 9 is interpreted as being drawn to the antibody of Claim 1 having a Kd equivalent to the parent antibody and being expressed in a cell-free wheat translation system.

Claim 20 is *interpreted* as being drawn to a labeled single chain antibody comprising a heavy and light chain of an antibody directly crosslinked through a linker with the linker comprising an amino acid sequence recognized by biotin ligase where the ligase binds a labeling substance to the linker and the linker is bound to the labeling substance, where the antibody is encoded by DNA and the DNA is transcribed and translated using a cell-free wheat translation system in the presence of a labeling substance and an enzyme that catalyzes disulfide bond exchange.

The claimed single chain antibodies were prima facie obvious at the time of the invention over Silber as evidenced Weiss and Pavlinkova in view of Fricker.

The interpretation of Silber as evidenced Weiss and Pavlinkova is discussed above under section 14. None of the references teach expressing the antibody protein in a cell-free wheat-based protein translation system. Fricker discloses producing a multimeric scFv complex under these conditions.

Fricker discloses scFV networks comprising an idiotype scFv attached to a first fluorescent polypeptide; and an anti-idiotype scFv which is attached to a second fluorescent polypeptide; and a linker which connects the two fluorescent polypeptides.

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Fricker discloses producing the probes in cell-free translation systems [0055] including wheat [0158].

One skilled in the art could have readily modified the single chain antibodies of Silber and/or of Pavlinkova to have been expressed in a wheat embryo-derived system in order to obtain a homogeneous, exogenous cell-free scFv isolate. One could have reasonably expected to have achieved the single chain antibodies because the reagents were available and the techniques for producing single chain antibodies much less the fusion proteins comprising labeling-substance modified scFvs were within ordinary skill of the art at the time of the invention based on the disclosures of Silber and/or of Pavlinkova and Fricker. Each of Silber and/or of Pavlinkova also appreciates the convenience of an internal or linker-associated label which facilitates purification or identification of the single chain antibody or which can be used to easily immobilize the antibody by binding of the label to its recognition site. Further because the single chain antibody of Silber and/or of Pavlinkova is a simplification of the "idiotype network" of Fricker or seemingly structurally less complex, one would have been further motivated to have combined the references and been assured of success in doing so to produce single chain antibodies expressed in wheat embryo translation systems in order to reduce the purification and processing steps ordinary associated with E. coli systems. For all of these reasons, the claimed antibody was prima facie obvious at the time of the invention over Silber and/or of Pavlinkova in view of Fricker.

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17. Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibling et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07).

Claims 21-23 are interpreted as being drawn to a method for producing an immobilized single chain antibody comprising any one of the following four antibodies 1) comprising a heavy and light chain crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker, 2) comprising a heavy and light chain variable regions crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker, 3) comprising a heavy and light chain crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker and the labeling substance is biotin, or 4) comprising a heavy and light chain variable regions crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker and the labeling substance is biotin, and where any one of the these antibodies binds to a substance recognizing the labeling substance when brought into contact with a reaction plate being coated with the substance (Claim 21), where two or more different kinds of immobilized antibodies are

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immobilized on the plate (Claim 22), and the labeling substance is biotin and the substance the labeling substance reacts with is streptavidin (Claim 24).

Claim 24 is interpreted as being drawn to an immobilized single chain antibody prepared by the method of Claim 21.

The claimed method for producing an immobilized single chain antibody and the immobilized single chain antibody were prima facie obvious at the time of the invention over Silber as evidenced Weiss and Pavlinkova.

The interpretation of Silber as evidenced by Weiss is discussed above under section 15. Silber further teaches developing a method for screening in vivo biotinylated anti-human IgGs from two different murine hybridomas. Silber does not disclose single chain antibodies (e.g., scFvs) being directly crosslinked with a linker where the BCCP domain is integrated into the structure but indicates that single chain Fvs (scFvs) which are smaller and generally expressed at higher levels in bacteria than Fab may be efficiently biotinylated in vivo by the methods. Pavlinkova teaches the immobilized antibody array comprising scFvs comprising a linker and a labeling substance.

The interpretation of Pavlinkova is discussed above under section 15.

One skilled in the art would have been motivated to have produced and been reasonably assured of success having produced the method for generating an immobilized single chain antibody and the immobilized single chain antibody over Silber as evidenced by Weiss and Pavlinkova. Each of the references teaches DNA-based methods for making and expressing antibody fragments comprising the VH and VL domains of a corresponding antibody which are disulfide linked and which comprise a

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region for biotinylation (Silber) or a biotinylation mimetic domain (Pavlinkova). Silber provides sufficient motivation to consider generating or modifying small antibody fragments for ease of selection where the antibody is directly bound to biotin during the intracellular expression process taking advantage of endogenous biotin ligase within the *E. coli* and by increasing the degree of biotinylation with a co-engineered biotin ligase. Because both references suggest or specifically teach generating scfvs, the ordinary artisan could have combined the methods in order to produce the modified scfv of Pavlinkova by introducing the BCCP domain of Silber into the construct especially in a region such as the linker being away from the variable domains to avoid steric hindrance with binding to antigen, and where multiple different scFvs directed against different antigens were produced based on Silber and further where the produced biotinylated antibody was bound to a surface coated streptavidin plate in order to create an array of immobilized biotinylated scfvs based on Pavlinkova. Thus the methods to generate a scfv comprising a linker containing the BCCP domain being recognized by biotin ligase, was obvious in view of Silber and Pavlinkova in order to retain antigen binding but to facilitate biotin labeling for antibody screening and selection and for producing immobilized antibodies. Expressed scFvs that are naturally biotinylated would eliminate in vitro chemical biotinylation procedures in order to avoid conditions that are deleterious for binding activity and the binding capacity is virtually identical to the parent antibody (Silber, p. 138, Col. 2, ¶1). Thus to generate the instant claimed methods for an immobilized antibody and the immobilized antibody itself would have been reasonably expected by the ordinary artisan because a similar method had already

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been generated by Pavlinkova where in view of Silber, the amount of biotinylation could be enhanced with the BCCP domain in the presence of increased biotin ligase expression. The claimed invention was prima facie obvious.

18. Claims 21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) as applied to claim 1 above, and further in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07).

The interpretation of Claim 21 is discussed above under section 17. Claim 28 is interpreted as the method being drawn to an immobilized antibody produced by the method of Claim 21 having the equivalent Kd as the parent antibody where the method uses a cell-free translation system.

The immobilized antibody produced by a method using a cell-free translation system was prima facie obvious at the time of the invention over Silber as evidenced Weiss and Pavlinkova and Fricker.

The interpretation of Silber as evidenced Weiss and Pavlinkova for the method of producing the immobilized antibody was discussed above under section 17. Silber as evidenced Weiss and Pavlinkova teach and appreciate that the methods can be used to express engineered constructs directed to different antigens and as immobilized arrays for screening and selecting the antibodies using streptavidin, but does not

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disclose production methods in a wheat-embryo derived cell-free translation system while Fricker does.

Fricker discloses scFV networks comprising an idiotype scFv attached to a first fluorescent polypeptide; and an anti-idiotype scFv which is attached to a second fluorescent polypeptide; and a linker which connects the two fluorescent polypeptides. Fricker discloses producing the probes in cell-free translation systems [0055] including wheat [0158].

One skilled in the art could have readily modified the immobilized single chain antibodies of Silber and/or of Pavlinkova to have been expressed in a wheat embryo-derived system in order to obtain a homogeneous, exogenous cell-free scFv isolate in order to be immobilized on a surface plate. One could have reasonably expected to have achieved the immobilized single chain antibodies because the reagents were available and the techniques for producing immobilized single chain antibodies much less the fusion proteins comprising labeling-substance modified scFvs were within ordinary skill of the art at the time of the invention based on the disclosures of Silber and/or of Pavlinkova and Fricker. Each of Silber and/or of Pavlinkova also appreciates the convenience of an internal or linker-associated label which facilitates purification or identification of the single chain antibody or which can be used to easily immobilize the antibody by binding of the label to its recognition site in order to avoid complicated in vitro biotinylation chemical reactions. Further because the immobilized single chain antibody of Silber and/or of Pavlinkova is a simplification of the "idiotype network" of Fricker or seemingly structurally less complex, one would have been further motivated

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to have combined the references and been assured of success in doing so to produce immobilized single chain antibodies expressed in wheat embryo translation systems in order to reduce the purification and processing steps ordinarily associated with *E. coli* systems. For all of these reasons, the claimed immobilized antibody was *prima facie* obvious at the time of the invention over Silber and/or of Pavlinkova in view of Fricker.

19. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07).

Claim 29 is *interpreted* as being drawn to a product-by-process claim for a labeled single chain antibody having a Kd equivalent to the parent antibody and produced a method where DNA encoding a heavy chain and a light chain against a specific antigen and a linker comprising a labeling substance being incorporated into a part of the linker, where the expressed protein comprises the heavy and light chains being linked by the linker, and where the DNA is subjected to transcription and translation in a wheat embryo, cell-free protein translation system in the presence of a labeling substance and an enzyme that catalyzes a disulfide bond exchange reaction.

The labeled single chain antibody product-by-process was *prima facie* obvious over Pavlinkova and Fricker.

Pavlinkova disclose scFv antibodies containing streptavidin-binding peptide or a biotin-like mimic peptide (BMP) where the scFv is modified to contain the BMP. The

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dimeric scFv comprises VL-linker-VH-linker-VL-linker-VH where the BMP having amino acid sequence SAWRHPQFGG was added to the carboxyl terminus of the VH region by adding the nucleotide sequence shown in figure 1 (Materials and Methods, p. 354, Col. 2, ¶2). One of ordinary skill in the art would reasonably interpret that the addition of the BMP to the C-terminus of the VH domain could occur at either VH domain for the dimeric scFV such as: VL-linker-VH-BMP-linker-VL-linker-VH or VL-linker-VH-BMP-linker-VL-linker-VH-BMP or VL-linker-VH-linker-VL-linker-VH-BMP absent a showing to the contrary. The first and second embodiments of the dimeric scFv would require that the labeling substance, BMP, bind to the linker vis-à-vis a fusion as taught by Pavlinkova. Pavlinkova teaches expressing the scFvs in Yeast expression systems, detecting the scFvs by ELISA where the single chain antibody would be immobilized, reacting the scFvs with streptavidin to form a complex. Pavlinkova teaches that another scFv-BMP molecule recognizing CA125, had also been generated by others, thus the insertion of a biotin-like or BMP labeling substance within the linker or binding to the linker vis-à-vis a fusion was already known in the art (p. 359, Col. 1, ¶2) and one could readily envisage the combination of scFv-BMP molecules. Pavlinkova teaches that the immunoreactivity of the single chain antibody was unchanged compared to the parent scFV (p. 359, Col.2, ¶2). Pavlinkova teaches that a labeling substance can block the binding sites or hinder the binding of the conjugate to the targeting moiety, but that insertion of the BMP into a strictly defined site ensures that the immunoreactivity is retained. It is noted that the labeling substance of the instant invention is not limited to the peptide of SEQ ID NO: 11 as shown in Figure 1 of the instant specification,

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therefore any biotin peptide or BMP as taught by Pavlinkova anticipates the claimed single chain antibody. Pavlinkova teaches and appreciates that the engineered construct assures consistency of quality and structure (p. 359, Col. 2, ¶2), but does not disclose production in a wheat-embryo derived cell-free translation system while Fricker does.

Fricker discloses scFV networks comprising an idiotype scFv attached to a first fluorescent polypeptide; and a anti-idiotype scFv which is attached to a second fluorescent polypeptide; and a linker which connects the two fluorescent polypeptides. Fricker discloses producing the probes in cell-free translation systems [0055] including wheat [0158].

One skilled in the art would have been motivated to have produced the instant claimed antibody based on the combined disclosures of Pavlinkova and Fricker. Both Pavlinkova and Fricker explicitly teach single chain antibodies scFvs having peptide linkers or spacers which further comprise or have inserted within or bound to the spacer/linker a labeling molecule such as polyhistidine tag or biotinylation peptide sequence (BMP). Both Pavlinkova and Fricker teach immobilization of the scFv in a solid plate. Fricker discloses cell-free translation of the antibodies and expression in wheat. Because Fricker discloses producing a multimeric scFv complex under these conditions, one skilled in the art could have readily modified the scFv of Pavlinkova to have been expressed in a wheat embryo-derived system in order to obtain a homogeneous, exogenous cell-free scFv isolate. One could have reasonably expected to have achieved the single chain antibodies because the reagents were available and

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the techniques for producing single chain antibodies much less the fusion proteins comprising labeling-substance modified scFvs were within ordinary skill of the art at the time of the invention based on the disclosures of Pavlinkova and Fricker. Each of the references also appreciates the convenience of an internal or linker-associated label which facilitates purification or identification of the single chain antibody or which can be used to easily immobilize the antibody by binding of the label to its recognition site. Further because the scFv of Pavlinkova is a simplification of the "idiotype network" of Fricker or seemingly structurally less complex, one would have been further motivated to have combined the references and been assured of success in doing so to produce single chain antibodies and expressed in wheat embryo translation systems. For all of these reasons, the claimed antibody was prima facie obvious at the time of the invention over Pavlinkova and Fricker.

Conclusion

20. No claims are allowed.

21. Sanatala et al. (J. Immunol. Methods 284:165-175 (2004)) is considered a relevant, post-filing date reference but not relied on by the examiner.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Lynn Bristol/
Examiner, Art Unit 1643
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